REMARKS

I. THE REJECTIONS UNDER 35 U.S.C. § 112, 1st ¶

The final Office Action rejects claims 26 and 28 under 35 U.S.C. § 112, first paragraph, for recitation of "each in separate pharmaceutically acceptable carrier" and "together in a single pharmaceutically acceptable carrier", respectively. In particular, the final Office Action asserts:

> [N]owhere in the disclosure is the combination where [in] the three drugs are provide[ed as] separate pharmaceutically acceptable carriers or in a single pharmaceutically acceptable carriers [is recited].

(Final Office Action at page 3). Applicants respectfully traverse the rejection.

Applicants submit that the specification provides adequate support for the combination as claimed in claims 26 and 28. See, the specification at, e.g., the paragraph bridging pages 13-14, which discloses:

> The active ingredients of the combinations of the present invention may be administered simultaneously, concurrently or sequentially. Simultaneous administration may be done by employing *a* ***unitary pharmaceutical formulation or separate pharmaceutical formulations***. In general, the combinations may be administered by topical, oral, rectal, intravenous, subcutaneous or intramuscular routes. For first line therapy of HIV infection, simultaneous administration employing a unitary pharmaceutical formulation is preferred.

Reconsideration and withdrawal of the rejection of claims 26 and 28 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

II. THE REJECTION UNDER 35 U.S.C. § 103

The Office Action rejects claims 1, 6, 19-21 and 25-29 under 35 U.S.C. § 103 as being obvious over WO03016306 in view of Peiperi et al., Tenofovir (Viread, PMPA), August 7, 2003 and Hazen et al., Journal of AIDS, 2003, 32:255-258, as evidenced by De Clercq, Il Farmaco, 1999, 54:26-45. Applicants respectfully traverse the rejection.

As reiterated by the Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (2007), the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(A) Determining the scope and content of the prior art;

(B) Ascertaining the differences between the claimed invention and the prior art;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Determining the obviousness or nonobviousness of the claimed subject matter.

Secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. The question of obviousness must be resolved on the basis of these factual determinations. While each case is different and must be decided on its own facts, the Graham factors, including secondary considerations when present, are the controlling inquiries in any obviousness analysis.

Applicants submit that the cited references do not disclose or suggest the combination as presently claimed, i.e., a combination comprising TMC278, tenofovir or its prodrug tenofovir disoproxil fumarate; and emtricitabine; wherein said TMC278, said tenofovir its prodrug tenofovir disoproxil fumarate and said emtricitabine are present in therapeutically effective amounts that can be administered once daily to treat HIV. The present specification discloses:

> WO 03/016306 specifically discloses m**ore than 250 pyrimidine derivative having HIV replication inhibiting properties** that act as non-nucleoside RT inhibitors (NNRTIs) having the ability to inhibit the replication both wild-type and of mutant strains. **One of said NNRTIs is 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]-benzonitrile (herein referred to as TMC278).** WO 03/016306 also discloses the methods to synthesize these compounds. It **further discloses combinations of said NNRTIs with other antiretrovirals, i.e. suramine, pentamidine, thymopentin, castanospermine, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate), zidovudine (3' azido-3'-deoxythymidine, AZT), didanosine (2',3'-di-deoxyinosine; ddI), zalcitabine (dideoxycytidine, ddC), lamivudine (2'-3'-dideoxy-3' thiacytidine, 3TC), stavudine (2',3'-didehydro-3'-deoxythymidine, d4T), abacavir, nevirapine (11 cyclopropyl-5,11-di¬hydro-4-methyl-6H-dipyrido-¬[3,2-b : 2',3'-e] [1,4]diazepin-6-one), efavirenz, delavirdine, TMC120, TMC125, tenofovir, (S) 8 chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)¬imidazo-[4,5,1 jk] [1,4]benzodiazepine-2(1H)-thione, -[(2-nitrophenyl)amino]-2,6-di¬chloro-benzene-acetamide, RO 5 3335, indinavir, ritonavir, saquinavir, lopinavir (ABT-378), nelfinavir, amprenavir, TMC126, BMS-232632, VX-175, T-20, T-1249, AMD-3100 and hydroxyurea.**

> **Notwithstanding existing combination therapy, there is still a need for improved antiretroviral therapy, more particularly AIDS therapy**. This need is particularly acute for therapy that is effective not only on wild type HIV virus, but also on the increasingly more common resistant HIV viruses. It is thus highly desirable especially for first line therapy to design a combination regimen with a low pill burden that limits or even suppresses the recurrence of drug resistant virus and which can be used and remains effective for a long term.

Amongst all of the possible combinations, Applicants were first to conceive of a triple combination of tenofovir, emtricitabine and TMC278. Also, Applicants were also first to conceive that the triple combination could be employed for once daily use. Such combination is highly desirable as it allows the suppression of HIV with a just one pill every day.

As recognized in the final Office Action,

> Guillemont does not teach the specific utility of the combination of the three drugs [T]MC278, Tenofovir and emtricitabine together in HIV treatment and does not teach once a day dosing of the combination.

(See final Office Action at page 7).

Although Peiperi discloses the use of tenofovir with antiretroviral agents such as lamivudine and efavirenz, it also does not disclose or suggest a combination of tenofovir with emtrictabine and/or TMC278.

Hazen et al., which discloses a study to assess the relative potencies of emtricitabine, lamivudine and zidovudine in primary cells (see, e.g., Abstract and pages 255-256), also does not disclose or suggest a combination of tenofovir, emtricitabine and TMC278.

De Clercq, which discloses general recommendations for HIV treatment (see, e.g., Table 3 at page 38), also does not disclose or suggest a combination of tenofovir, emtricitabine and TMC278. In fact, De Clercq itself discloses that:

> In vivo, various triple-drug combinations containing NNRTI's, NRTI's and/or PI's ***may*** result in an effective viral suppression and ensuing immune recovery. However, this so-called HAART (highly active antiretroviral therapy) ***may also fail, and this necessitates the design of new and more effective drugs and drug cocktails***.

(See Abstract (emphasis added)).

Reconsideration and withdrawal of the rejection of claims 1, 6, 19-21 and 25-29 under 35 U.S.C. § 103 WO03016306 in view of Peiperi et al., Tenofovir (Viread, PMPA), August 7, 2003 and Hazen et al., Journal of AIDS, 2003, 32:255-258, as evidenced by Clercq, II Farmaco, 1999, 54:26-45, are respectfully requested.

III. CONCLUSION

Early consideration and prompt allowance of the claims are respectfully requested.

Respectfully submitted,

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